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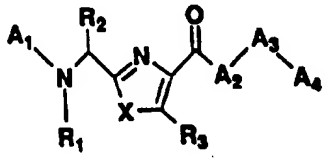

(I)

(57) Abstract

Azole derivatives of formula (I) are disclosed as useful in treating platelet-mediated thrombotic disorders.

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AZOLE PEPTIDOMIMETICS AS THROMBIN RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

Thrombin is an important serine protease in hemostasis and thrombosis. One of the key actions of thrombin is receptor activation. A functional human thrombin receptor, cloned by Coughlin in 1991 (T.-K. Vu, *Cell* **1991**, *64*, 1057), was found to be a member of the G-protein coupled receptor (GPCR) superfamily. The receptor activation putatively occurs by N-terminal recognition and proteolytic cleavage at the Arg-41/Ser-42 peptide bond to reveal a truncated N-terminus. This new receptor sequence, which has an SFLLRN (Ser-Phe-Leu-Leu-Arg-Asn) N-terminus acting as a tethered ligand to recognize a site on the receptor, can trigger activation and signal transduction leading to platelet aggregation. Since 1991, two other protease-activated receptors with extensive homology to the thrombin receptor, "PAR-2" (S. Nystedt, *Proc. Natl. Acac. Sci USA* **1994**, *91*, 9208) and "PAR-3" (H. Ishihara, *Nature* **1997**, *386*, 502), were cloned, and found to be activated by similar N-terminal hexapeptide sequences. Thrombin receptor (PAR-1) specific antibody-induced blockade of the platelet thrombin receptor has shown efficacy against arterial thrombosis in vivo (J. J. Cook *Circulation* **1995**, *91*, 2961). Hence, antagonists of the thrombin receptor based on SFLLRN are useful in antagonizing these protease-activated receptors and as such may be used to treat platelet mediated thrombotic disorders such as myocardial infarction, stroke, restenosis, angina, atherosclerosis, and ischemic attacks by virtue of their ability to prevent platelet aggregation.

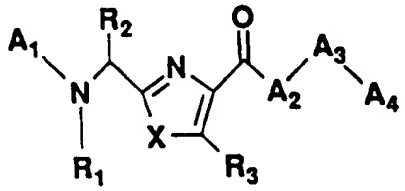
The thrombin receptor has also been identified on other cell types: endothelial, fibroblast, osteosarcoma, smooth muscle, and neuronal/glia. Thrombin activation of endothelial cells upregulates P-selectin to induce polymorphonuclear leukocyte adhesion - an inflammatory response of the vessel wall (Y. Sugama, J. Cell Biol. 1992, 119, 935). In fibroblasts, thrombin receptor activation induces proliferation and transmission of mitogenic signals (D. T. Hung, *J. Cell Biol.* **1992**, *116*, 827). Thrombin has

been implicated in osteoblast proliferation through its activation of osteoblast cells (D. N. Tatakis, *Biochem. Biophys. Res. Commun.* **1991**, *174*, 181). Thrombin has been implicated in the regulation and retraction of neurons (K. Jalink, *J. Cell. Biol.* **1992**, *118*, 411). Therefore, in this context, the antagonist compounds of this invention may also be useful against inflammation, restenosis, osteoporosis, and neurodegenerative disorders.

The compounds of the present invention are azole peptidomimetics represented by the general formula (I) below. Azole-containing cyclic peptides have been synthesized to be employed as cytotoxic agents (C. Boden, *Tetrahedron Lett.* **1994**, *35*, 8271). By contrast, the azole peptidomimetics of the present invention are strictly acyclic with activity against the thrombin receptor. Azole-based dolastatin analogues have been prepared as antitumor agents (K.Sakakibara, PCT Int. Appl., 31 pp., WO9633212). These compounds contain a 4-thiazole-alkylamide C-terminus, whereas the compounds of the present invention require at least two amino acid residues C-terminal to the 4-thiazole carboxamide for activity against the thrombin receptor. Similarly, azole endothelin antagonists have been prepared which contain a 4-thiazole-carboxylic acid C-terminus (T. von Geldern, *J. Med. Chem.* **1996**, *39*, 957).

DISCLOSURE OF THE INVENTION

The present invention is directed to compounds represented by the following general formula (I):



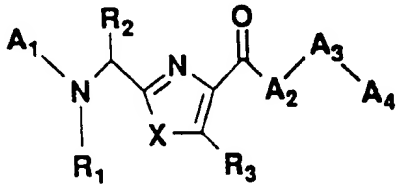
(I)

wherein A1, A2, A3, A4, R1, R2, R3, and X are as hereinafter defined. The compounds of the present invention are platelet aggregation inhibitors and as such are useful in treating platelet-mediated thrombotic disorders such as arterial and venous thrombosis, acute myocardial infarction, reocclusion following thrombolytic therapy and angioplasty, inflammation, unstable

angina, and a variety of vaso-occlusive disorders. These compounds are also useful as antithrombotics in conjunction with fibrinolytic therapy (e.g., t-PA or streptokinase). Pharmaceutical compositions containing such compounds as the active ingredient as well as methods of preparing the compounds are also part of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

More particularly, the present invention is directed to compounds of the following formula (I):



(I)

wherein A_1 is an amino acid residue selected from Sar, Gly, His, His(CH_2Ph), Ile Ser, Thr, β-Ala, or Ala. A_1 may also be a C_2-C_6-acyl group such as, for example, acetyl, propionyl or butyryl or a C_1-C_8-alkyl group such as, for example, methyl, ethyl, propyl or butyl;

wherein A_2 is an alkyl amino acid residue selected from Cha, Leu, Ile, Asp, and Glu or an amino alkyl amino acid residue such as Lys, His, Orn, homoArg and Arg;

wherein A_3 is an amino alkyl amino acid residue selected from Lys, His, Orn, Arg and homoArg;

wherein A_4 is an arylalkyl residue selected from Phe and Tyr or an aralkylamino group such as benzylamino or a phenethylamino group;

wherein R_1 is selected from H or alkyl;

wherein R_2 is an aryl, substituted aryl, heteroaryl,substituted heteroaryl, aralkyl or substituted aralkyl group, however R_2 is preferably aralkyl;

wherein R_3 is selected from H or alkyl;

wherein X is selected from S, O, or NR_4, wherein R_4 is selected from H or alkyl;

and the pharmaceutically acceptable salts thereof.

As used herein, unless otherwise noted alkyl and alkoxy whether used alone or as part of a substituent group, include straight and branched chains having 1-8 carbons. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, *n*-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, *n*-hexyl, 2-hexyl, 2-methylpentyl and the like. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. Acyl radicals are residues having 2-6 carbon atoms derived from an organic acid by removal of the hydroxyl group.

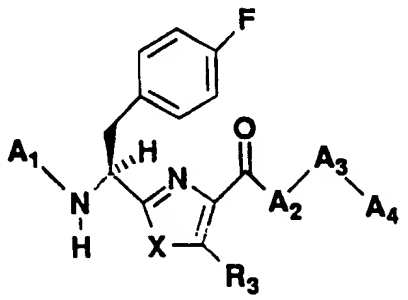
The terms "aryl", "heteroaryl", "substituted aryl" and "substituted heteroaryl" as used herein alone or in combination with other terms indicates aromatic or heteroaromatic groups such as phenyl, naphthyl, pyridyl, thienyl, furanyl, or quinolinyl wherein the substituent is a halo, alkyl, amino, nitro or alkoxy group. The term "aralkyl" means an alkyl group substituted with an aryl group.

Unless otherwise indicated, the other substituent on the carbon to which R_2 is attached is hydrogen.

The compounds of the present invention may also be present in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salt generally takes a form in which the basic nitrogen is protonated with an inorganic or organic acid. Representative organic or inorganic acids include hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benezenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic.

Particularly preferred compounds of the present invention include those compounds shown in Table I, where the amino acids bear the "L" absolute configuration unless denoted otherwise.

TABLE I

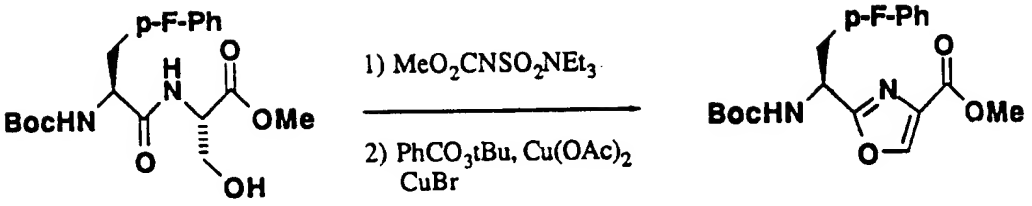


#	R3	A1	A2	A3	A4	X
1	H	Sar	Cha	Arg	$NHCH_2Ph$	O
2	H	β-Ala	Cha	Arg	$NHCH_2Ph$	O
3	H	Sar	Cha	Arg	$NH(CH_2)_2Ph$	S
4	H	Sar	Cha	hArg	$Phe\text{-}NH_2$	S
5	H	Ile	Cha	Arg	$Phe\text{-}NH_2$	S
6	H	Sar	Lys	Arg	$NH(CH_2)_2Ph$	S
7	Me	Sar	Cha	Arg	$NHCH_2Ph$	O
8	Me	$His(CH_2Ph)$	Cha	Arg	$NHCH_2Ph$	O
9	Me	Ac	Cha	Arg	$NHCH_2Ph$	O
10	Me	Me_2	Cha	Arg	$NHCH_2Ph$	O

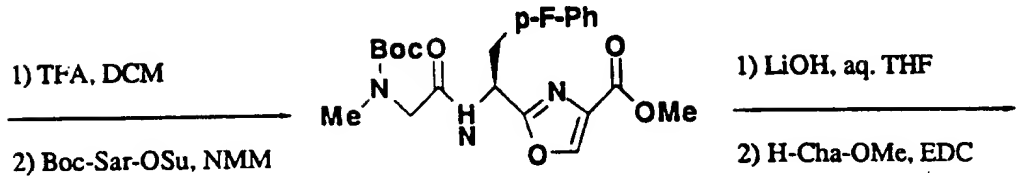
The antagonists of the present invention may be prepared as shown in Scheme AA. Protected oxazole intermediates (AA2) can be prepared in two steps from the corresponding dipeptide (AA1) by Burgess Reagent-mediated cyclization to the oxazoline and then oxidation with, for example, t-butyl peroxybenzoate to give the oxazole (AA2). Dipeptides such as AA1 can be synthesized from the corresponding protected amino acids using standard solution-phase peptide coupling conditions utilizing EDC as the activating agent, NMM as the base and DCM as the solvent. Standard peptide methods are employed to complete the synthesis (e.g. compound 1). Boc removal from AA2 utilizing an acid such as, for example,TFA or HCl and coupling with Boc-Sar-OSu affords AA3. The ester is then saponified

with a base such as, for example, lithium hydroxide or any alkali metal or alkaline earth metal base and the carboxylic acid product is coupled with H-Cha-OMe to give AA4. Saponification of AA4 with a base, such as lithium hydroxide, for example, coupling with H-Arg(Pmc)-NHBn (EDC), and deprotection with TFA affords the product (**1**). The aforementioned Arg reagent, and other Arg amides in general, can be prepared in two steps from Fmoc-Arg(Pmc)-OH by EDC-mediated coupling with benzylamine and then Fmoc removal with 20% piperidine in dioxane. Although the Scheme is used to illustrate the preparation of those compounds wherein R_2 is p-F-Ph, all of the compounds of the present invention can be prepared using the method illustrated in Scheme AA by utilizing an appropriately substituted oxazole, thiazole or imidazole as the starting material. Intermediate azoles other than oxazole AA2 can be prepared according to the methods exemplified in Schemes AB, AC, and AD.

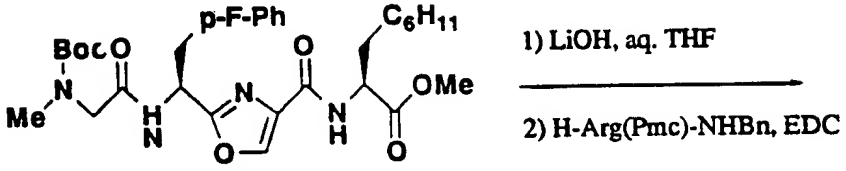
SCHEME AA



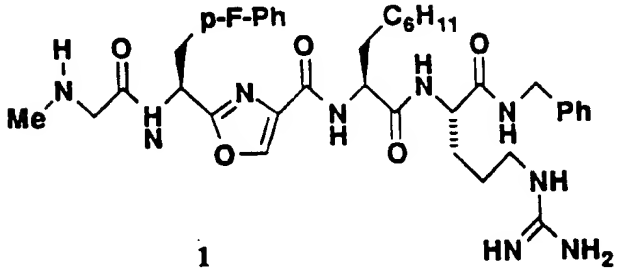
AA1 AA2



AA3

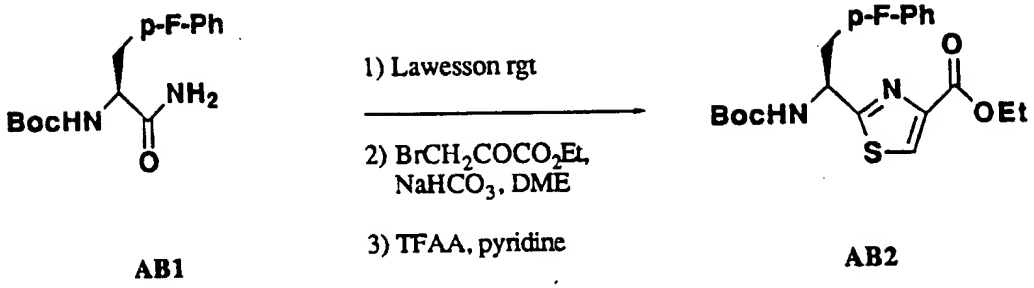


AA4



1

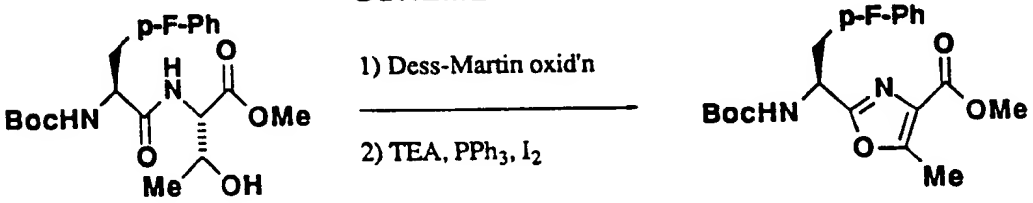
SCHEME AB



AB1 AB2

The thiazole intermediate AB2 can be prepared in three steps from an amino acid residue (AB1) using Hantzsch cyclization methodology (Scheme AB). AB1 is converted to the corresponding thioamide using Lawesson's Reagent. The thioamide is then alkylated with ethyl 3-bromopyruvate, and the product is cyclized with trifluoroacetic anhydride to give AB2. Those compounds of the present invention wherein X is S can be prepared from AB2 using standard peptide coupling procedures as exemplified in Scheme AA.

SCHEME AC



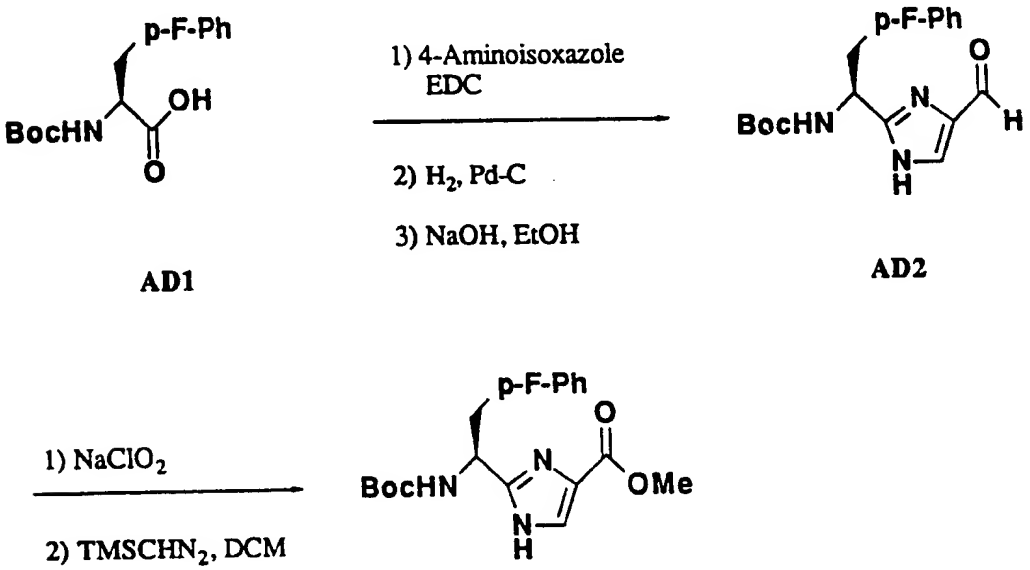
AC1 AC2

The 5-methyl-oxazole intermediate AC2 can be prepared in two steps from a dipeptide (AC1) (Scheme AC). AC1 is converted to the corresponding methyl ketone using the Dess-Martin reagent and the methyl ketone is then cyclized with triphenylphosphine/iodine to give AC2. In the case of compound **10**, the *N,N*-dimethyl-p-F-Phe derivative is prepared by reductive alkylation with, for example, formaldehyde/sodium triacetoxyborohydride following Boc removal with, for example, TFA from AC2, and then the synthesis completed as shown in Scheme AA.

Those starting materials wherein X is NR_4 can be synthesized according to methods known to those skilled in the art. (S. K. Thompson, *J.*

Med. Chem. 1994, *37*, 3100). In this procedure, EDC-mediated coupling of Boc-p-Phe-OH (AD1) with 4-amino-isoxazole followed by hydrogenation (H_2/Pd-C) and sodium hydroxide-mediated cyclization provides the corresponding 2-substituted-imidazole-4-carboxaldehyde (AD2, Scheme AD). Oxidation of this aldehyde to the corresponding imidazole-4-carboxylic acid using standard methods ($NaClO_2$) and trimethylsilyldiazomethane esterification provides the imidazole AD3. Those compounds of the present invention wherein X is NR_4 can be prepared from AD3 using standard peptide coupling procedures as exemplified in Scheme AA. Alkylation of the imidazole by generally known techniques produces those compounds of the invention wherein R_4 is alkyl.

Scheme AD



AD1 **AD2**

AD3

To prepare the pharmaceutical compositions of this invention, one or more compounds of formula (I) or salt thereof of the invention as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as, for

example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules, caplets, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, of from about 0.03 mg to 100 mg/kg (preferred 0.1-30 mg/kg) and may be given at a dosage of from about 0.1-300 mg/kg/day (preferred 1-50 mg/kg/day). The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

BIOLOGY

The compounds of the present invention interrupt platelet activation induced by thrombin's proteolytic cleavage of its platelet surface receptor, and thereby inhibit platelet aggregation. Such compounds are, therefore, useful in treating platelet-mediated thrombotic disorders such as arterial and venous thrombosis, acute myocardial infarction, reocclusion following thrombolytic therapy and angioplasty, and a variety of vaso-occlusive disorders.

IN VITRO THROMBIN RECEPTOR BINDING ASSAY.

CHRF membranes (Jones, *Biochim. Biophys. Acta* **1992**, *1136*, 272) are thawed from -70°C, centrifuged at maximum speed for 5 min, washed twice with binding buffer (50 mM HEPES containing 5 mM $MgCl_2$ and 0.1% BSA), and re-suspended in binding buffer (25 µg/100 mL). 100 µl of membranes are added to the 24-Wallac plates and delivered to the Tomtech apparatus. In a typical experiment, 6 µl of samples (from a 125 µg/mL intermediary plate, 20%DMSO) and 44 µl buffer are delivered to the plates (final conc. of compounds is 3.7 µg/mL, 0.6% DMSO). Similarly, 6 µl 20%DMSO and 44 µl buffer are delivered to both column 1 (NSB) and column 12 (TB). 10 µl Ser-pFPhe-Har-Leu-Har-Lys-Tyr-NH_2 (721-40; 500 µM in deionized water) is added to column 1. 50 µl tritiated 721-40 (specific activity 46 Ci/mmol) is added to all the wells. The plates are mixed well for 20 seconds, incubated for 30 min, and then harvested with 10 mM HEPES/138 mM NaCl using the Skatron harvester. The filters (GF/C Brandel FPXLR 296) are presoaked 3 h in 0.5% polyethylenimine in HEPES/0.1 M N-acetylglucosamine) are set in saran wrap and dried for 3 min in the microwave, and placed in sample bags (Wallac 1450-432). 4.5 mL scintillation fluid (Wallac, Betaplate Scint 1205-440) is added. The bags are sealed, placed in filter cassettes (Wallac 1450-104), and analyzed on the microbeta counter.

IN VITRO INHIBITION OF THROMBIN-INDUCED GEL-FILTERED PLATELET AGGREGATION ASSAY.

The percentage of platelet aggregation is calculated as an increase in light transmission of compound-treated platelet concentrate vs. control-treated platelet concentrate. Human blood is obtained from drug free, normal donors in tubes containing 0.13 M sodium citrate. Platelet rich plasma (PRP) is collected by centrifugation of whole blood at 200 x g for 10 min at 25°C. The PRP (5 mL) is gel filtered through Sepharose 2B (bed volume 50 mL), and the platelet count is adjusted to $2x10^7$ platelets per sample. The following constituents are added to a siliconized cuvette: concentrated platelet filtrate and Tyrode's buffer (0.14 M NaCl, 0.0027 M KCl, 0.012 M $NaHCO_3$, 0.76 mM Na_2HPO4, 0.0055 M glucose, 2 mg/mL

BSA and 5.0 mM HEPES @ pH 7.4) in an amount equal to 350 µl, 50 µl of 20 mM calcium and 50 µl of the test compound. Aggregation is monitored in a BIODATA aggregometer for the 3 min following the addition of agonist (thrombin 50 µl of 1 unit/mL).

Table II shows the biological activity of the compounds of the present invention. The table contains IC_{50} values (µM) of the compounds in a thrombin receptor binding assay, and IC_{50} values (µM) against platelet aggregation stimulated by two agonists, thrombin or SFLLRN-NH_2 (TRAP).

TABLE II

Biological Activity

	Thr Receptor Binding	Platelet Aggregation**	
Compound	IC_{50}*	IC_{50} Thr*	IC_{50} TRAP*
1	2.0	25	10
2	8.2	10	7
3	35.0	12	0.6
4	5.0	45	3
5	3.5	43	9
6	15.5	26	4
7	7.0	19	22
8	30.0	13	5
9	31.0	24	11
10	NT	11	17

* µM

** Thrombin-induced aggregation of gel-filtered platelets in µM.

EXAMPLES

Protected amino acids were purchased from Fluka Chemical or Bachem Bioscience Inc. All other chemicals were purchased from Aldrich Chemical Company, Inc. High field ^1H NMR spectra were recorded on a Bruker AC-360 spectrometer at 360 MHz, and coupling constants are given in Herz. Melting points were determined on a Mel-Temp II melting point

apparatus and are uncorrected. Microanalyses were performed at Robertson Microlit Laboratories, Inc., Madison, New Jersey.

In the examples and throughout this application, the following abbreviations have the meanings recited hereinafter:

Ac	Acetyl
Bn	Benzyl
Boc	t-Butoxycarbonyl
Cbz	Benzyloxycarbonyl
CP	compound
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIC	Diisopropylcarbodiimide
DIEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	N, N-Dimethylformamide
EDC	Ethyl dimethylaminopropylcarbodiimide
EDTA	Ethylenediaminetetraacetic acid
Et_2O	Diethyl ether
Fmoc	9-Fluorenylmethoxycarbonyl
HOBT	Hydroxybenzotriazole
i-Pr	Isopropyl
NMM	N-Methylmorpholine
OSu	N-Oxysuccinimide
Pmc	2,2,5,7,8-Pentamethylchroman-6-sulfonyl
PTSA	p-Toluenesulfonic acid
RT	room temperature
TFA	Trifluoroacetic acid

Amino acid abbreviations are defined below:

Ala	Alanine
β-Ala	beta-Alanine
Arg	Arginine
Asp	Aspartic Acid
Cha	Cyclohexylalanine
p-F-Phe	4-Fluorophenylalanine

Glu	Glutamic Acid
Gly	Glycine
hArg	Homoarginine (homoArg)
His	Histidine
Ile	Isoleucine
Leu	Leucine
Lys	Lysine
Or	Ornithine
Phe	Phenylalanine
Sar	Sarcosine
Ser	Serine
Thr	Threonine
Tyr	Tyrosine

Methyl 2-[1(S)-t-butoxycarbonylamino-2-(4-fluorophenyl)ethyl]oxazole-4-carboxylate (AA2)

To a solution of Boc-*p*-F-Phe-OH (0.018 mol), DCM (200 mL), H-Ser-OMe (0.018 mol), HOBT (10 mg), and EDC•HCl (0.036 mol) at 5°C was added NMM (0.036 mol). The reaction was stirred for 3.5 h, diluted with sat'd NH_4Cl (30 mL). The layers were separated, and the organic layer was washed with sat'd $NaHCO_3$ (30 mL), dried (Na_2SO_4), and evaporated to give a white powder (5.9 g). The powder was dissolved in DME (100 mL), treated with (methoxycarbonylsulfamoyl) triethylammonium hydroxide (0.015 mol), and heated at reflux for 1 h. The reaction was cooled to RT, diluted with EtOAc (150 mL) and sat'd $NaHCO_3$ (30 mL), and the layers separated. The organic layer was dried (Na_2SO_4) and evaporated to give a white solid (4.8 g). The solid was dissolved in benzene (140 mL), treated with $Cu(OAc)_2$ (0.014 mol), CuBr (0.014 mol), and t-butyl peroxybenzoate (0.020 mol), and heated at reflux for 5 h. The reaction was cooled, diluted with EtOAc (50 mL) and sat'd $NaHCO_3$ (10 mL), and filtered. The layers of the filtrate were separated, and the organic layer dried and evaporated to a brown oil. The oil was purified over silica gel (2% MeOH/DCM) to give AA2 as a gold solid (1.75 g): ^1H NMR ($CDCl_3$) δ 8.12 (s, 1 H), 7.6 (m, 1 H), 6.9 (m, 4 H), 5.2 (m, 1 H), 3.91 (s, 3 H), 3.2 (m, 2 H), 1.40 (s, 9 H); FAB-MS m/e 365 (MH+).

The following examples describe the invention in greater detail and are intended to illustrate the invention but not to limit it.

EXAMPLE 1

2-[1(S)-Sarcosineamido-2-(4-fluorophenyl)ethyl]oxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide (1)

Intermediate AA2 (4.1 mmol) was dissolved in DCM (10 mL) and TFA (12 mL) and stirred for 1 h. The solution was concentrated to give a brown oil, and the oil triturated with hexane (50 mL). The oil was dissolved in DCM (60 mL), treated with Boc-Sar-OSu (4.1 mmol) and NMM (12.3 mmol), and stirred for 24 h. The reaction mixture was diluted with sat'd NH_4Cl (15 mL) and the layers separated. The organic layer was washed with sat'd $NaHCO_3$ (20 mL), dried (Na_2SO_4), evaporated, and purified by silica gel chromatography (2%MeOH/DCM) to give a brown oil (AA3, 1.0 g). AA3 (2.1 mmol) was dissolved in THF (10 mL), cooled to 5°C, treated with aq. LiOH (4 mmol/20 mL water), and stirred for 2 h. The reaction was acidified with citric acid (0.5 g) and extracted with $CHCl_3$ (2x70 mL). The organic materials were dried (Na_2SO_4) and evaporated to give a gold foam (0.85 g). The foam (2.0 mmol) was dissolved in DCM (60 mL) and treated with H-Cha-OMe•HCl (2.0 mmol), HOBT (10 mg), EDC•HCl (3.0 mmol), and NMM (4.0 mmol). This mixture was stirred for 2 h, diluted with sat'd NH_4Cl (20 mL), and the layers separated. The organic layer was dried, evaporated, and purified by silica gel chromatography (3% MeOH/DCM) to afford a gold oil (AA4, 1.0 g; FAB-MS m/e 589, MH+). AA4 (1.7 mmol) was dissolved in THF (10 mL), cooled to 5°C, treated with aq. LiOH (3.4 mmol/20 mL water), and stirred for 2 h. The reaction was acidified with citric acid (0.5 g) and extracted with $CHCl_3$ (2x70 mL). The organic materials were dried (Na_2SO_4) and evaporated to give a gold oil (0.71 g). The oil (1.2 mmol) was dissolved in DCM (60 mL) and treated with H-Arg(Pmc)-$NHCH_2Ph$ (1.2 mmol), HOBT (10 mg), EDC•HCl (2.4 mmol), and NMM (1.2 mmol). This mixture was stirred for 2 h, diluted with sat'd NH_4Cl (20 mL), and the layers separated. The organic layer was dried (Na_2SO_4), evaporated, and purified by silica gel chromatography (7% EtOH/DCM) to afford a clear glass (0.90 g). The glass was dissolved in DCM (5 mL) and anisole (0.5 mL), treated with TFA (10 mL), and stirred for 2.5 h. The solution was evaporated, and the resultant

green oil triturated with Et_2O (4x30 mL), dried (Na_2SO_4), and isolated as a white powder (0.90 g): mp 127-130°C; FAB-MS m/e 720 (MH^+); $[\alpha]^{24}D$ - 21.8° (c 0.28, MeOH). Anal. calcd. for $C_{37}H_{50}N_9O_5F \cdot 2.0$ TFA (947.91): C, 51.95; H, 5.53; N, 13.30. Found: C, 51.53; H, 5.78; N, 13.05.

EXAMPLE 2

2-[1(S)-β-Alanineamido-2-(4-fluorophenyl)ethyl]oxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide (2)

Compound **2** was prepared using the method described in example 1. Intermediate AA2 (2.2 mmol) was deprotected with TFA and then reacted with H-β-Ala-OSu (2.2 mmol) as described. Compound **2** was isolated as a white powder (0.21 g): mp 108-112°C; FAB-MS m/e 720 (MH^+). Anal. calcd. for $C_{37}H_{50}N_9O_5F \cdot 2.0$ TFA $\cdot 0.5$ H_2O (956.93): C, 51.46; H, 5.58; N, 13.17; KF, 0.91. Found: C, 51.41; H, 5.95; N, 13.20; KF, 0.88.

Ethyl 2-[1(S)-t-butoxycarbonylamino-2-(4-fluorophenyl)ethyl]thiazole-4-carboxylate (AB2)

To a solution of AB1 (14.9 mmol) in dioxane (60 mL) was added Lawesson's reagent (8.9 mmol). This mixture was stirred for 3 h, filtered, and the filtrate evaporated and purified by silica gel chromatography (2% MeOH/DCM) to afford the thioamide (3.9 g). The thioamide (13.1 mmol) was dissolved in DME (80 mL), treated with $NaHCO_3$ (0.10 mol) and ethyl bromopyruvate (39.3 mmol), and stirred for 20 min. The mixture was cooled to 5°C, treated with a solution of TFAA (52.4 mmol), pyridine (0.10 mol), and DME (10 mL), and the ice bath removed. This mixture was stirred for 17 h, filtered, concentrated, diluted with DCM, and washed with water. The organic layer was dried (Na_2SO_4) and purified by silica gel chromatography (1.5% MeOH/DCM) to afford AB2 as a white foam (4.6 g): ^1H NMR ($CDCl_3$) δ 8.08 (s, 1 H), 7.1 (m, 2 H), 6.9 (m, 2 H), 5.3 (m, 2 H), 4.4 (q, 2 H), 3.2 (m, 2 H), 1.5 (t, 3 H), 1.40 (s, 9 H); FAB-MS m/e 395 (MH^+).

EXAMPLE 3

2-[1(S)-Sarcosineamido-2-(4-fluorophenyl)ethyl]thiazole-4-carboxy-cyclohexylalanyl-arginine phenethylamide (3)

Compound **3** was prepared by the method described for compound **1**. Intermediate AB1 (1.2 mmol) was dissolved in DCM (10 mL) and TFA (12 mL) and the resultant solution was stirred for 1 h. The solution was then concentrated to give a brown oil, and the oil triturated with hexane (50 mL). The oil was dissolved in DCM (60 mL), treated with Boc-Sar-OSu (1 mmol) and NMM (3 mmol), and stirred for 24 h. The reaction was diluted with sat'd NH_4Cl (15 mL) and the layers separated. The organic layer was washed with sat'd $NaHCO_3$ (20 mL), dried (Na_2SO_4), evaporated, and purified by silica gel chromatography (2%MeOH/DCM) to give an oil. The oil was dissolved in THF (10 mL), cooled to 5°C, treated with aq. LiOH (1 mmol/6 mL water), and stirred for 2 h. The reaction was acidified with citric acid (0.2 g) and extracted with $CHCl_3$ (2x70 mL). The organic materials were dried (Na_2SO_4) and evaporated to give a foam. The foam (0.5 mmol) was dissolved in DCM (60 mL) and treated with H-Cha-OMe•HCl (0.5 mmol), HOBT (3 mg), EDC•HCl (1 mmol), and NMM (1.5 mmol). This mixture was stirred for 2 h, diluted with sat'd NH_4Cl (20 mL), and the layers separated. The organic layer was dried (Na_2SO_4), evaporated, and purified by silica gel chromatography (3% MeOH/DCM) to afford a clear oil. The oil was dissolved in THF (5 mL), cooled to 5°C, treated with aq. LiOH (0.2 mmol/4 mL water), and stirred for 2 h. The reaction was acidified with citric acid (0.5 g) and extracted with $CHCl_3$ (2x50 mL). The organics were dried (Na_2SO_4) and evaporated to give a gold oil (0.71 g). The oil (1.2 mmol) was dissolved in DCM (60 mL) and treated with H-Arg(Pmc)-$NHCH_2CH_2Ph$ (1.2 mmol), HOBT (10 mg), EDC•HCl (2.4 mmol), and NMM (1.2 mmol). This mixture was stirred for 2 h, diluted with sat'd NH_4Cl (20 mL), and the layers separated. The organic layer was dried, evaporated, and purified by silica gel chromatography (7% EtOH/DCM) to afford a clear glass (0.3 g). The glass was dissolved in DCM (5 mL) and anisole (0.5 mL), treated with TFA (10 mL), and stirred for 2.5 h. The solution was evaporated, and the resultant brown oil triturated with Et_2O (4x30 mL), dried, and isolated as a beige powder (0.093 g): ^1H NMR (DMSO-d_6) δ 9.2 (m, 2 H), 8.4 (d, 1 H), 8.33 (s, 1 H), 8.2 (m, 1 H), 8.1 (m, 1 H), 7.6 (m, 1 H), 6.9-7.4 (m, 9 H), 5.4 (m, 1 H),

4.6 (m, 1 H), 4.2 (m, 1 H), 3.6 (q, 2 H), 3.0-3.5 (m, 6 H), 2.7 (m, 2 H), 2.5 (m, 2 H), 2.39 (s, 3 H), 1.3-1.9 (m, 10 H), 0.8-1.3 (m, 10 H); FAB-MS m/e 750 (MH^+).

EXAMPLE 4

2-[1(S)-Sarcosineamido-2-(4-fluorophenyl)ethyl]triazole-4-carboxy-cyclohexylalanyl-homoarginyl-phenylalanineamide (4)

Compound **4** was prepared by the method described in example 3 from AB2 (1.0 mmol) and Boc-Sar-OSu (1.0 mmol) ,and isolated as a tan powder (0.021 g): ^1H NMR (DMSO-d_6) δ 8.38 (s, 1 H), 8.0 (d, 1 H), 7.9 (d, 1 H), 7.5 (m, 1 H), 7.0-7.4 (m, 9 H), 5.4 (m, 1 H), 4.6 (m, 1 H), 4.4 (m, 1 H), 4.2 (m, 1 H), 3.7 (q, 2 H), 3.4 (m, 4 H), 3.1 (m, 4 H), 2.8 (m, 2 H), 2.47 (s, 3 H), 1.7 (m, 1 H), 1.3-1.8 (m, 8 H), 0.8-1.4 (m, 16 H); FAB-MS m/e 807 (MH^+).

EXAMPLE 5

2-[1(S)-Isoleucineamido-2-(4-fluorophenyl)ethyl]triazole-4-carboxy-cyclohexylalanyl-arginyl-phenylalanineamide (5)

Compound **5** was prepared aby the method described in example 3 from AB2 (1.3 mmol) and Boc-Ile-OH (1.3 mmol), and isolated as a pale yellow powder (0.079 g): ^1H NMR (DMSO-d_6) δ 9.2 (m, 1 H), 8.8 (m, 1 H), 8.72 (s, 1 H), 7.7-8.1 (m, 7 H), 7.6 (m, 1 H), 6.8-7.5 (m, 9 H), 5.4 (m, 1 H), 4.6 (m, 1 H), 4.4 (m, 1 H), 4.3 (m, 1 H), 3.7 (m, 2 H), 3.6 (m, 1 H), 3.4 (m, 2 H), 2.7-3.2 (m, 6 H), 1.8 (m, 2 H), 1.0-1.7 (m, 18 H), 0.9 (d, 3 H), 0.8 (t, 3 H); FAB-MS m/e 835 (MH^+).

EXAMPLE 6

2-[1(S)-Sarcosineamido-2-(4-fluorophenyl)ethyl]thiazole-4-carboxy-lysyl-arginine phenethylamide (6)

Compound 6 was prepared by the method described in example 3 from AB2 (1.4 mmol) and Boc-Sar-OSu (1.4 mmol), and isolated as a tan powder (0.099 g): FAB-MS m/e 725 (MH^+).

Methyl 2-[1(S)-t-butoxycarbonylamino-2-(4-fluorophenyl)ethyl]-5-methyloxazole-4-carboxylate (AC2)

Dipeptide AC1 (12.6 mmol), prepared by the method described for the preparation of Boc-*p*-F-Phe-Ser-OMe in example AA2, was dissolved in DCM (125 mL) and water (0.2 mL) and treated with 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benzodioxol-3(1H)-one (Dess-Martin reagent; 15.1 mmol). The reaction was stirred for 30 min, diluted with DCM (100 mL), and washed with sat'd $NaHCO_3$ (2x40 mL), dried, and evaporated. The residue was purified by silica gel chromatography (30% EtOAc/hexane) to give a ketone. A solution of DCM (70 mL), PPh_3 (8.3 mmol), and TEA (16.5 mmol) was treated with the ketone (8.3 mmol) and stirred for 5 min. The mixture was washed with aq. $Na_2S_2O_3$ and sat'd $NaHCO_3$, and the organic layer dried, evaporated, and purified by silica gel chromatography (25%EtOAc/hexane) to give AC2 as a white foam (2.5 g): ^1H NMR ($CDCl_3$) δ 7.1 (m, 2 H), 6.9 (m, 2 H), 5.1 (m, 2 H), 3.92 (s, 3 H), 3.2 (m, 2 H), 2.60 (s, 3 H), 1.40 (s, 9 H); FAB-MS m/e 379 (MH^+).

EXAMPLE 7

2-[1(S)-Sarcosineamido-2-(4-fluorophenyl)ethyl]-5-methyloxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide (7)

Compound 7 was prepared by the method described for the preparation of compound 1. Intermediate AC1 (1.3 mmol) was dissolved in DCM (10 mL) and TFA (12 mL) and the solution was stirred for 1 h. The solution was

concentrated to give a tan oil, and the oil triturated with hexane (50 mL). The oil was dissolved in DCM (60 mL), treated with Boc-Sar-OSu (1.3 mmol) and NMM (4 mmol), and stirred for 24 h. The reaction was diluted with sat'd NH_4Cl (15 mL) and the layers separated. The organic layer was washed with sat'd $NaHCO_3$ (20 mL), dried (Na_2SO_4), evaporated, and purified by silica gel chromatography (2%MeOH/DCM) to give an oil. The oil was dissolved in THF (10 mL), cooled to 5°C, treated with aq. LiOH (1 mmol/6 mL water), and the mixture stirred for 2 h. The reaction mixture was acidified with citric acid (0.2 g) and extracted with $CHCl_3$ (2x70 mL). The organic materials were dried (Na_2SO_4) and evaporated to give a foam. The foam (0.6 mmol) was dissolved in DCM (60 mL) and the solution was treated with H-Cha-OMe•HCl (0.6 mmol), HOBT (3 mg), EDC•HCl (1 mmol), and NMM (1.5 mmol). This mixture was stirred for 2 h, diluted with sat'd NH_4Cl (15 mL), and the layers separated. The organic layer was dried (Na_2SO_4), evaporated, and the residue was purified by silica gel chromatography (3% MeOH/DCM) to afford a tan oil. The oil was dissolved in THF (5 mL), cooled to 5°C, treated with aq. LiOH (0.2 mmol/4 mL water), and the mixture was stirred for 2 h. The reaction mixture was then was acidified with citric acid (0.5 g) and extracted with $CHCl_3$ (2x50 mL). The organic materials were dried (Na_2SO_4) and evaporated to give a glass (0.71 g). The glass (1.2 mmol) was dissolved in DCM (60 mL) and the solution was treated with H-Arg(Pmc)-NHBn (1.2 mmol), HOBT (5 mg), EDC•HCl (2.4 mmol), and NMM (1.2 mmol). This mixture was stirred for 2 h, diluted with sat'd NH_4Cl (20 mL), and the layers separated. The organic layer was dried (Na_2SO_4), evaporated, and the residue was purified by silica gel chromatography (7% EtOH/DCM) to afford a clear glass (0.3 g). The glass was dissolved in DCM (5 mL) and anisole (0.5 mL), the resultant solution was treated with TFA (10 mL), and stirred for 2.5 h. The solution was evaporated, and the resultant glass triturated with Et_2O (4x25 mL), dried (Na_2SO_4), and isolated as a white powder (0.10 g): mp 117-121°C; FAB-MS m/e 734 (MH^+). Anal. calcd. for $C_{38}H_{52}N_9O_5F \cdot 2.0$ TFA $\cdot$ 0.5 H_2O (970.94): C, 51.96; H, 5.71; N, 12.98; KF, 0.94. Found: C, 51.88; H, 5.89; N, 12.60; KF, 1.0.

EXAMPLE 8

2-[1(S)-N(tau)-Benzyl-histidineamido-2-(4-fluorophenyl)ethyl]-5-methyloxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide (8)

Compound 8 was prepared by the method described for the preparation of compound 7 from AC2 (1.1 mmol) and Boc-His(Bn)-OH (1.1 mmol), and isolated as a white powder (0.083 g): mp 101-106°C; FAB-MS m/e 890 (MH^+). Anal. calcd. for $C_{48}H_{60}N_{11}O_5F$ • 2.6 TFA • 0.8 anisole • 1.0 H_2O (1294.5): C, 54.61; H, 5.53; N, 11.90; KF, 1.39. Found: C, 54.23; H, 5.44; N, 11.96; KF, 1.75.

EXAMPLE 9

2-[1(S)-Acetamido-2-(4-fluorophenyl)ethyl]-5-methyloxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide (9)

Compound 9 was prepared by the method described for the preparation of compound 7 from AC2 (1.2 mmol) and acetyl chloride (1.2 mmol), and isolated as a white powder (0.10 g): mp 111-116°C; FAB-MS m/e 705 (MH^+). Anal. calcd. for $C_{37}H_{49}N_8O_5F$ • 1.0 TFA • 1.0 anisole • 1.0 H_2O (901.78): C, 57.54; H, 6.35; N, 12.43; KF, 2.0. Found: C, 57.71; H, 6.27; N, 12.49; KF, 2.32.

EXAMPLE 10

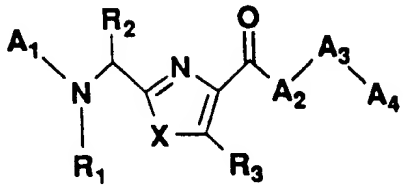
2-[1(S)-N,N-Dimethyl-2-(4-fluorophenyl)ethyl]-5-methyloxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide (10)

Compound **10**, preparedby the method described for the peparation of compound **7**, was synthesized via methyl 2-[1(S)-N,N-dimethyl-2-(4-fluorophenyl)ethyl]-5-methyloxazole-4-carboxylate as follows. Intermediate AC2 (1.0 mmol) was deprotected of the Boc group with TFA as described. The primary amine TFA salt was partitioned between DCM (50 mL) and sat'd $NaHCO_3$ (15 mL), and the layers separated. The organic layer was dried (Na_2SO_4) and evaporated to a glass. The glass was dissolved in DCE

(10 mL) and 37% formaldehyde (0.23 mL) at RT and then treated with sodium triacetoxyborohydride (4.0 mmol). The mixture was stirred for 18 h, diluted with DCM (50 mL), and washed with sat'd $NaHCO_3$ (10 mL). The organic layer was dried (Na_2SO_4), evaporated, and the resultant foam purified by silica gel chromatography (1.5%MeOH/DCM) to afford methyl 2-[1(S)-N,N-dimethyl-2-(4-fluorophenyl)ethyl]-5-methyloxazole-4-carboxylate as a glass (0.24 g). This glass was used to prepare **10** aby the method described in example **7**. Compound **10** was isolated as a tan powder (0.088 g): mp 115°C; FAB-MS m/e 691 (MH^+). Anal. calcd. for $C_{37}H_{51}N_8O_4F \cdot 2.0$ TFA $\cdot$ 2.1 H_2O (956.75): C, 51.47; H, 6.03; N, 11.71; KF, 3.95. Found: C, 51.24; H, 6.28; N, 12.09; KF, 4.23.

WE CLAIM:

1. A compound represented by the general formula (I):



(I)

wherein A_1 is an amino acid residue selected from Sar, Gly, His, His(CH_2Ph), Ile, Ser, Thr, β-Ala, Ala, a C_2-C_6-acyl group and a C_1-C_8-alkyl group;

wherein A_2 is an alkyl amino acid residue selected from Cha, Leu, Ile, Asp and Glu or an aminoalkyl amino acid residue selected from Lys, His, Orn, homoArg and Arg;

wherein A_3 is an amino alkyl amino acid residue selected from Lys, His, Orn, Arg and homoArg;

wherein A_4 is an arylalkyl residue selected from Phe and Tyr or an aralkylamino group;

wherein R_1 is selected from H or alkyl;

wherein R_2 is aryl, substituted aryl, heteroaryl, substituted heteroaryl aralkyl or substituted aralkyl;

wherein R_3 is H or alkyl;

wherein X is selected from S, O, or NR_4, wherein R_4 is selected from H or alkyl;

and the pharmaceutically acceptable salts thereof.

2. The compound of claim 1 wherein X is O.

3. The compound of claim 1 wherein X is S.

4. The compound of claim 1 wherein X is NR_4.

5. The compound of claim 1, wherein:
A_1 is an amino acid residue;
A_2 is an alkyl amino acid residue;
A_3 is an aminoalkyl amino acid residue;
A_4 is aralkyl;
R_1 is H or alkyl;
R_2 is aryl or substituted aryl;
R_3 is H or alkyl; and
X is S, O, or NR_4;
and the pharmaceutically acceptable salts thereof.

6. The compound of claim 5 wherein X is O.

7. The compound of claim 5 wherein X is S.

8. The compound of claim 5 wherein X is NR_4.

9. The compound of claim 1, selected from any of:

2-[1(S)-Sarcosineamido-2-(4-fluorophenyl)ethyl]oxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide,

2-[1(S)-β-Alanineamido-2-(4-fluorophenyl)ethyl]oxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide,

2-[1(S)-Sarcosineamido-2-(4-fluorophenyl)ethyl]thiazole-4-carboxy-cyclohexylalanyl-arginine phenethylamide,

2-[1(S)-Sarcosineamido-2-(4-fluorophenyl)ethyl]triazole-4-carboxy-cyclohexylalanyl-homoarginyl-phenylalanineamide,

2-[1(S)-Isoleucineamido-2-(4-fluorophenyl)ethyl]triazole-4-carboxy-cyclohexylalanyl-arginyl-phenylalanineamide,

2-[1(S)-Sarcosineamido-2-(4-fluorophenyl)ethyl]thiazole-4-carboxy-lysyl-arginine phenethylamide,

2-[1(S)-Sarcosineamido-2-(4-fluorophenyl)ethyl]-5-methyloxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide,

2-[1(S)-N(tau)-Benzyl-histidineamido-2-(4-fluorophenyl)ethyl]-5-methyloxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide,

2-[1(S)-Acetamido-2-(4-fluorophenyl)ethyl]-5-methyloxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide and

2-[1(S)-N,N-Dimethyl-2-(4-fluorophenyl)ethyl]-5-methyloxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide.

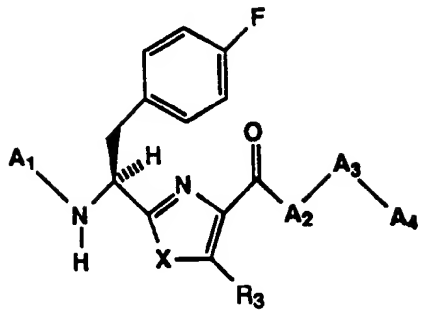
10. A compound of claim 9 selected from the group consisting of:

2-[1(S)-Sarcosineamido-2-(4-fluorophenyl)ethyl]oxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide,

2-[1(S)-β-Alanineamido-2-(4-fluorophenyl)ethyl]oxazole-4-carboxy-cyclohexylalanyl-arginine benzylamide and

2-[1(S)-Sarcosineamido-2-(4-fluorophenyl)ethyl]thiazole-4-carboxy-cyclohexylalanyl-arginine phenethylamide.

11. A compound of claim 1 of the formula:



wherein A_1 is an amino acid residue selected from Sar, Gly, His, His(CH_2Ph), Ile, Ser, Thr, β-Ala, Ala, a C_2-C_6-acyl group or a C_1-C_8-alkyl group;

wherein A_2 is an alkyl amino acid residue selected from Cha, Leu, Ile, Asp and an amino alkyl amino acid residue selected from Lys, His, Orn, homoAarg and Arg;

wherein A_3 is an amino alkyl amino acid residue selected from Lys, His, Orn, Arg and homoArg;

wherein A_4 is an arylalkyl residue selected from Phe, Tyr or an aralkylamino group;

wherein R_3 is H or alkyl;

wherein X is selected from S, O, or NR_4, wherein R_4 is selected from H or alkyl;

and the pharmaceutically acceptable salts thereof.

12. The compound of claim 11 wherein X is O.

13. The compound of claim 11 wherein X is S.

14. The compound of claim 11 wherein X is NR_4.

15. The compound of claim 11 wherein:

A_1 is an amino acid residue;

A_2 is an alkyl amino acid residue;

A_3 is an amino alkyl amino acid residue;

A_4 is arylalkyl or aralyklamino;

R_3 is H; and

X is S, O or NR_4.

16. The compound of claim 15 wherein X is O.

17. The compound of claim 15 wherein X is S.

18. The compound of claim 15 wherein X is NR_4.

19. The compound of claim 1 wherein the pharmaceutically acceptable salt is the trifluoroacetate.

20. A composition for treating platelet-mediated thrombotic disorders comprising the compound of claim 1 in an effective amount for treating such disorders in combination with a pharmaceutically acceptable carrier.

21. A method of treating platelet-mediated thrombotic disorders comprising administering to a patient afflicted with such disorder an effective amount of the compound of claim 1 to treat such disorder.

22. The method of claim 21, wherein the amount is 0.03 mg to 100 mg/kg/day.

INTERNATIONAL SEARCH REPORT

	International Application No PCT/US 99/02627

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/097 A61K38/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	HOEKSTRA W J ET AL: "Thrombin receptor (PAR-1) antagonists. Heterocycle-based peptidomimetics of the SFLLR agonist motif" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 13, 7 July 1998, page 1649-1654 XP004137101 see the whole document ---	1-22
A	DATABASE WPI Section Ch, Week 9601 Derwent Publications Ltd., London, GB; Class B03, AN 96-006941 XP002103727 & JP 07 285952 A (FUJISAWA PHARM CO LTD) , 31 October 1995 see abstract ---	1-22
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 1999	10/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/02627

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	M S BERNATOWICZ ET AL: "Development of potent thrombin receptor antagonist peptides" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 25, 6 December 1996, pages 4879-4887, XP002095053 see the whole document	1-22
A	SCARBOROUGH, R. M. ET AL: "Thrombin receptor antagonists derived from "tethered ligand" agonist peptides" 1994 , PEPT.: CHEM., STRUCT. BIOL., PROC. AM. PEPT. SYMP., 13TH (1994), MEETING DATE 1993, 695-7. EDITOR(S): HODGES, ROBERT S.;SMITH, JOHN A. PUBLISHER: ESCOM, LEIDEN, NETH. CODEN: 60LXAW XP002103726 see the whole document	1-22
A	WO 94 03479 A (COR THERAPEUTICS INC ;SCARBOROUGH ROBERT M (US)) 17 February 1994 see the whole document	1-22
A	VON GELDERN T W ET AL: "Azole endothelin antagonists. 1. A receptor model explains an unusual structure-activity profile." JOURNAL OF MEDICINAL CHEMISTRY, (1996 FEB 16) 39 (4) 957-67. JOURNAL CODE: JOF. ISSN: 0022-2623., XP002103725 United States see the whole document	

1

INTERNATIONAL SEARCH REPORT

.nternational application No.
PCT/US 99/ 02627

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 21 and 22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
PCT/US 99/02627

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9403479 A	17-02-1994	AU 669922 B	27-06-1996
		AU 4668593 A	03-03-1994
		CA 2140543 A	17-02-1994
		EP 0656008 A	07-06-1995
		JP 2675438 B	12-11-1997
		JP 7506115 T	06-07-1995
		SG 49772 A	15-06-1998
		US 5866681 A	02-02-1999